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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,809	07/21/2003	S. Ananth Karumanchi	01948/088004	6646

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EXAMINER	
DANG, IAN D	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Interview Summary	Application No.	Applicant(s)	
	10/624,809	KARUMANCHI ET AL.	
	Examiner	Art Unit	
	Ian Dang	1647	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Ian Dang*.

(2) *Brenda Brumback*.

(3)*Kristina Bieker-Brady and Kimya Harris*.

(4)*Ananth Karumanchi*.

Date of Interview: *06 November 2006*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☒ Yes e)☐ No.
If Yes, brief description: *Illustration depicting the disease model*.

Claim(s) discussed: *41-69*.

Identification of prior art discussed: *Charnock-Jones (WO 98/28006)*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *We discussed amendents to overcome the 112 First paragraph rejection (Written Description) regarding claims 44-69, the 112 First paragraph rejection (Enablement) regarding claims 41-69, 112 Second paragraph rejection regarding claims 45-47, 57-67, and 50-67, and the 102 rejection regarding claims 43, 45, 46,49, 56-60, 62-65. No agreement regarding the rejected claims was reached during the interview.*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews

Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

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Telephone 617-428-0200
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617-428-7046

Date: November 3, 2006

To: Examiner Ian Dang

Facsimile No.: 1-571-273-5014

From: Kristina Bieker-Brady, Ph.D.

Re: U.S. Patent Application No.: 10/624,809
METHODS OF DIAGNOSING AND TREATING PRE-ECLAMPSIA AND ECLAMPSIA
Our Reference: 01948/088004

Pages: 11 - pages including cover sheet

Message: Per our discussion today, I am attaching a working draft of the proposed claim amendments and a proposed agenda for our interview on Monday, November 6. We look forward to meeting you on Monday.

S. Ananth Karumanchi et al.
U.S.S.N. 10/624,809 (Our Ref No: 01948/088004)
Filed on July 21, 2003
METHODS OF DIAGNOSING AND TREATING
PRE-ECLAMPSIA OR ECLAMPSIA

Proposed Agenda for Interview on November 6, 2006

Persons present:
Supervisor Brenda Brumback
Examiner Ian Dang
Dr. Kristina Bicker-Brady, Reg. No. 39,109
Dr. Kimya Harris, Reg. No. 57,172
Dr. S. Ananth Karumanchi

I. Current Status

The claimed invention provides methods for diagnosing pre-eclampsia and eclampsia in a subject, that include measuring the levels of sFlt-1, free PlGF, or free VEGF in a sample from the subject.

Claims 41-69 are pending and have been examined in the Office Action mailed on June 30, 2006. Claims 1-10, 13-21, 23, 27-32 are cancelled and claims 11-12, 22, 24-26, and 33-41 are withdrawn. A review of the current rejections and Applicants' proposed resolutions are provided below.

II. Claims 44-69 are rejected under § 112, first paragraph for lack of written description.

Issue: The Office states that the genus of VEGF molecules is not adequately described.

Proposed Resolution: Applicants propose amending claims 44 and 50 to recite the limitation that "said free VEGF is a VEGF polypeptide that has the ability to bind to sFlt-1." This provides a specific functional attribute for VEGF that can be readily assayed and that is described in the specification.

Support: At page 28, lines 1-4, the specification states, "While the detailed description presented herein refers specifically to sFlt-1, VEGF, or PlGF, it will be clear to one skilled in the art that the detailed description can also apply to sFlt-1, VEGF, or PlGF family members, isoforms, and/or variants, and to growth factors shown to bind sFlt-1."

Page 4, lines 22-25, "In various embodiments of the above aspects, the candidate compound is a growth factor such as vascular endothelial growth factor (VEGF), including all isoforms such as VEGF189, VEGF121, or VEGF165; placental growth factor (PlGF), including all isoforms; or fragments thereof."

III. Claims 41-69 are rejected under § 112, first paragraph for lack of enablement.

A. Issue: The Office states that the specification does not enable additional non-human subjects. (Clams 41-69)

Proposed Resolution: Applicants propose amending the claims to recite "human subjects" in each of the independent claims (claims 41-45, 48, and 50).

B. Issue: The Office states that the specification does not enable cerebrospinal fluid or amniotic fluid. (Claims 41 and 45-69)

Proposed resolution: Applicants propose deleting cerebrospinal fluid from claims 65. Applicants will provide evidence for the enablement of amniotic fluid and other sample types.

C. Issue: The Office states that the specification does not enable the diagnosis of HELLP, IUGR, or SGA. (Claims 68 and 69)

Proposed resolution: Applicants propose amending claim 68 to depend from claims 45, 49, and 50 and canceling claim 69.

The role of pre-eclampsia and eclampsia in HELLP, IUGR, and SGA will be discussed.

D. Issue: The Office states that the specification does not enable endothelial cells, leukocytes, monocytes, and cells derived from the placenta because the Office asserts that there are no working examples for measuring PlGF, sFlt-1 or VEGF levels in these cells. (Claims 41, 44, 45, 50, 64, and 66)

Proposed resolution: Applicants propose amending claim 66 and 67 to depend only from the claims that recite methods that include relative levels (e.g., claims 45 and 50). Claim 67 was not rejected but Applicants propose amendments for consistency.

IV. Claims 45-47, 57-67, and 50-67 are rejected under § 112, second paragraph for indefiniteness.

Issue: The Office states that the claims do not provide a clear link between the method of diagnosing a subject with pre-eclampsia or eclampsia and what constitutes a diagnosis.

Proposed resolution: Applicants propose amending claims 45 and 50 to recite the limitation that an increase of at least 10% in the level of sFlt-1 or a decrease of at least 10% in the level of free VEGF or free PlGF relative to a reference diagnoses the subject as having or having a propensity to develop pre-eclampsia or eclampsia. Claims 46 and 47, and 49 include the use of the metric and comparing the metric to a reference sample. For further clarity, Applicants propose amending claims 46, 47, and 49 to include the limitations that a difference of at least 10% between the subject metric and the reference metric diagnoses the subject as having or having a propensity to develop pre-eclampsia or eclampsia.

IV. Claims 43, 45, 46, 49, 56-60, 62-65 are rejected under § 102(b) for anticipation by Charnock-Jones (WO 98/28006, published July 2, 1998).

Issue: The Office characterizes Charnock-Jones as teaching the detection of significantly lower concentrations of PlGF in pre-eclamptic women as compared to healthy controls. In addition, the Office states that Charnock-Jones teaches a method for a method for diagnosing pre-eclampsia that includes measuring the levels of at least two of sFlt-1, free VEGF, and PlGF polypeptides and that the levels can be compared to control subjects who are normotensive pregnant women.

Proposed response: Applicants will review a diagram depicting differences between Charnock-Jones model and Applicants' model with respect to sFlt-1 and VEGF.

WORKING **DRAFT** OF PROPOSED CLAIM AMENDMENTS

Claims 1-10, 13-21, 23, 27-32, 51-53, 57, and 69 have been cancelled.

Claims 11-21, 22, 24-26, and 33-40 have been withdrawn.

41. (Currently amended) A method of diagnosing a human subject as having, or having a propensity to develop, pre-eclampsia or eclampsia, said method comprising measuring the level of sFlt-1 polypeptide in a sample from said subject, wherein a level of sFlt-1 polypeptide greater than 2 ng/ml diagnoses said subject as having, or having a propensity to develop, pre-eclampsia or eclampsia.

42. (Currently amended) A method of diagnosing a human subject as having, or having a propensity to develop, pre-eclampsia or eclampsia, said method comprising measuring the level of free PlGF polypeptide in a serum sample from said subject, wherein said free PlGF is a PlGF polypeptide that has the ability to bind to sFlt-1, and wherein said subject is pregnant and a level of free PlGF polypeptide less than 150 pg/ml serum at 13-16 weeks of pregnancy diagnoses said subject as having, or having a propensity to develop, pre-eclampsia or eclampsia.

43. (Currently amended) A method of diagnosing a human subject as having, or having a propensity to develop, pre-eclampsia or eclampsia, said method comprising measuring the level of free PlGF polypeptide in a serum sample from said subject, wherein said free PlGF is a polypeptide that has the ability to bind to sFlt-1, and wherein said subject is pregnant and a level of free

PlGF polypeptide less than 400 pg/ml serum at mid-gestation diagnoses said subject as having, or having a propensity to develop, pre-eclampsia or eclampsia.

44. (Currently amended) A method of diagnosing a human subject as having, or having a propensity to develop, pre-eclampsia or eclampsia, said method comprising measuring the level of free VEGF polypeptide in a sample from said subject, wherein said free VEGF is a VEGF polypeptide that has the ability to bind to sFlt-1, and wherein said subject is pregnant and a level of free VEGF polypeptide less than 5 pg/ml serum diagnoses said subject as having, or having a propensity to develop, pre-eclampsia or eclampsia. 12

45. (Currently amended) A method of diagnosing a human subject as having, or having a propensity to develop, pre-eclampsia or eclampsia, said method comprising measuring the levels of at least two of sFlt-1, free VEGF, and free PlGF polypeptide in a sample from said subject, wherein said free VEGF is a VEGF polypeptide that has the ability to bind to sFlt-1 and wherein said free PlGF polypeptide is a polypeptide that has the ability to bind to sFlt-1, and comparing the level to the level of at least two of sFlt-1, free VEGF, or free PlGF polypeptide in a reference, and wherein an increase of at least 10% in the level of sFlt-1 or a decrease of at least 10% in the level of free VEGF or free PlGF polypeptide relative to said reference diagnoses said subject as having, or having a propensity to develop, pre-eclampsia or eclampsia.

spec/cont p 11 line p 19

46. (Currently amended) The method of claim 45, further comprising ~~calculating the relationship between said levels of sFlt-1, free VEGF, and free PlGF using a metric~~ wherein said method comprises measuring the level of sFlt-1 and at least one of free VEGF and free PlGF, and wherein said method further comprises calculating the relationship between said level of sFlt-1 and said at least one of free VEGF and free PlGF using a metric, wherein an increase of at least

10% in the level of said sFlt-1 relative to at least one of said free VEGF and free PlGF level in said metric from said subject sample as compared to said metric from a reference sample diagnoses said subject as having, or having a propensity to develop, pre-eclampsia or eclampsia.

47. (Currently amended) The method of claim 46, wherein said metric is comprises a pre-eclampsia anti-angiogenic index (PAAI):[sFlt-1/ free VEGF + free PlGF], ~~wherein~~ and an increase of at least 10% in said PAAI in said subject sample as compared to ~~a normal~~ said reference is a diagnostic indicator of pre-eclampsia or eclampsia.

48. (Currently amended) ~~The method of claim 47,~~ A method of diagnosing a human subject as having, or having a propensity to develop, pre-eclampsia or eclampsia, said method comprising:

(a) measuring the levels of sFlt-1, free VEGF, and free PlGF polypeptides in a sample from a subject, wherein said free VEGF is a VEGF polypeptide that has the ability to bind to sFlt-1 and wherein said free PlGF polypeptide is a polypeptide that has the ability to bind sFlt-1; and

(b) calculating the relationship between said levels of sFlt-1, free VEGF, and free PlGF using a ~~PAAI~~ metric, wherein said metric is a pre-eclampsia anti-angiogenic index (PAAI):[sFlt-1/ free VEGF + free PlGF], and wherein a PAAI value greater than 20 in the subject sample is a diagnostic indicator of pre-eclampsia or eclampsia.

49. (Currently amended) The method of claim 46, wherein said metric ~~is~~ comprises sFlt-1/free PlGF and an increase of at least 10% in the sFlt-1/free PlGF from said subject sample as compared to said reference is a diagnostic indicator of pre-eclampsia or eclampsia.

50. (Currently amended) A method of diagnosing a human subject as having, or having a propensity to develop, pre-eclampsia or eclampsia, said method comprising measuring the level of at least one of sFlt-1, free VEGF, or free PlGF polypeptide in a sample from a subject, wherein said free VEGF is a VEGF polypeptide that has the ability to bind to sFlt-1 and wherein said free PlGF polypeptide is a polypeptide that has the ability to bind sFlt-1, and comparing the level to the level of sFlt-1, free VEGF, or free PlGF polypeptide in a reference, and wherein an increase of at least 10% in the level of sFlt-1 or a decrease of at least 10% in the level of free VEGF or free PlGF polypeptide relative to said reference diagnoses said subject as having, or having a propensity to develop, pre-eclampsia or eclampsia.

54. (Currently amended) The method of claim ~~52~~ 46, 47, 48, or 49, wherein said metric further comprises the body mass index or gestational age of the subject.

55. (Currently amended) The method of claim 45, 46, 47, 49, or 50 ~~or~~ 52, wherein said reference is a prior sample or level from said subject.

56. (Currently amended) The method of claim 45, 46, 47, 49, or 50 ~~or~~ ~~52~~, wherein said reference is a sample taken from a control subject not having pre-eclampsia or eclampsia.

58. (Currently amended) The method of claim 41, 44, 45, 46, 47, 48, 49, or 50, wherein said subject is in the first trimester of pregnancy.

59. (Currently amended) The method of claim 41, 44, 45, 46, 47, 48, 49, or 50, wherein said subject is in the second trimester of pregnancy.

60. (Currently amended) The method of claim 41, 44, 45, 46, 47, 48, 49, or 50, wherein said subject is in the third trimester of pregnancy.

61. (Currently amended) The method of claim ~~41, 44,~~ 41-45, 48, 49, or 50, wherein said subject is 13-16 weeks pregnant.

62. (Currently amended) The method of claim 41, 42, 43, 44, 45, 48, or 50, wherein said measuring is done using an immunological assay.

63. (Previously presented) The method of claim 62, wherein said immunological assay is an ELISA.

64. (Currently amended) The method of claim 41, 44, 45, 46, 47, 48, 49, or 50, wherein said sample is a bodily fluid~~, cell, or tissue~~ of said subject in which said sFlt-1, free VEGF, or free PlGF is normally detectable.

65. (Currently amended) The method of claim 64, wherein said bodily fluid is selected from the group consisting of urine, amniotic fluid, serum, and plasma~~, or cerebrospinal fluid~~.

66. (Currently amended) The method of claim ~~64~~ 45 or 50, wherein said sample is a cell or a tissue from said subject ~~cell is selected from the group consisting of an endothelial cell, leukocyte, a monocyte, and~~ a cell derived ~~from the placenta~~.

67. (Currently amended) The method of claim ~~64~~ 66, wherein said tissue is a placental tissue.

68. (Currently amended) ~~A method of~~ The method of any one of claims 45, 49, or 50, wherein said subject is further diagnosed ~~diagnosing a subject as~~ having, or having a propensity to develop, mild pre-eclampsia, severe pre-eclampsia, or pre-eclampsia associated with HELLP, IUGR, or SGA~~, said method comprising measuring the level of sFlt-1, free VEGF, or free PlGF polypeptide in a sample from said subject~~.

70. (New) The method of claim 41, 45, 46, 47, 48, 49, or 50, wherein said sFlt-1 is the level of free, bound, or total sFlt-1.

71. (New) The method of claim 45 or 50, wherein an increase of at least 50% in the level of sFlt-1 or a decrease of at least 50% in the level of free VEGF or free PlGF polypeptide relative to said reference diagnoses said subject as having, or having a propensity to develop, pre-eclampsia or eclampsia.

72. (New) The method of claim 71, wherein an increase of at least 90% in the level of sFlt-1 or a decrease of at least 90% in the level of free VEGF or free PlGF polypeptide relative to said reference diagnoses said subject as having, or having a propensity to develop, pre-eclampsia or eclampsia.

73. (New) The method of claim 47, wherein an increase of at least 50% in said PAAI in said subject sample as compared to said reference is a diagnostic indicator of pre-eclampsia or eclampsia.

74. (New) The method of claim 73, wherein an increase of at least 90% in said PAAI in said subject sample as compared to said reference is a diagnostic indicator of pre-eclampsia or eclampsia.

75. (New) The method of claim 49, wherein an increase of at least 50%

in said sFlt-1/free PlGF in said subject sample as compared to said reference is a diagnostic indicator of pre-eclampsia or eclampsia.

76. (New) The method of claim 75, wherein an increase of at least 90% in said sFlt-1/free PlGF in said subject sample as compared to said reference is a diagnostic indicator of pre-eclampsia or eclampsia.

77. (New) The method of claim 42 or 43, said method further comprising measuring the level of sFlt-1 in said subject sample, wherein a level of sFlt-1 polypeptide greater than 2 ng/ml diagnoses said subject as having, or having a propensity to develop, pre-eclampsia or eclampsia.

78. (New) The method of claim 45, said method comprising measuring the levels of sFlt-1 and free PlGF polypeptides.

79. (New) The method of claim 66, wherein said cell is selected from the group consisting of an endothelial cell, a leukocyte, a monocyte, and a cell derived from the placenta.